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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/530,580 | 10/10/2000 | JEAN-PHILIPPE ROCHER | P19428 | 3575 |

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| EXAMINER | |
|---|---|
| ROBINSON, BINTA M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1625 | |

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/530,580 | ROCHER ET AL. | |
| | Examiner | Art Unit | |
| | Binta M. Robinson | 1625 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-19 is/are pending in the application.

4a) Of the above claim(s) 19 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/7/00, 7/12/02.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**Detailed Action**

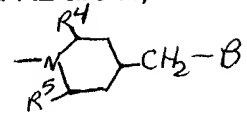
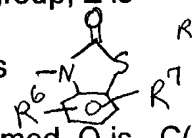
The elected species and elected group is noted at the paper filed 2/2/04.

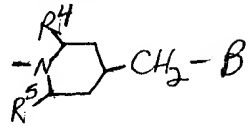
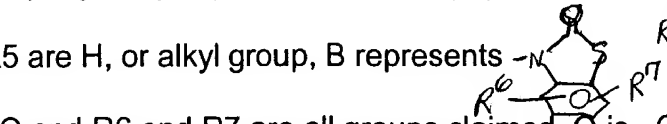
In a telephone conversation with Attorney Arnold Turk on 4/8/04, Attorney Turk indicated that the examiner could clarify the restriction requirement, restrict out claim 19 into a separate group invention, revise the elected group I so that it reads on the elected species and issue an action on the case, examining the elected group I invention, so as to advance prosecution of the case. Attorney Turk indicated that the clarified restriction requirement would still be traversed in the next office action. In view of applicant's comments in the Election with Traverse filed 2/2/04, the restriction requirement is clarified below:

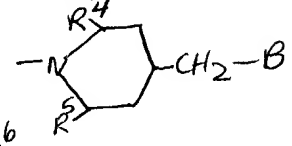
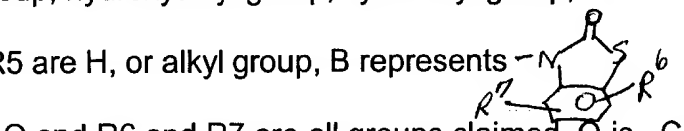
Restriction is required under 35 U.S.C. 121 and 372.

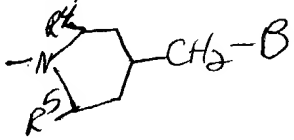
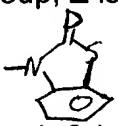
This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

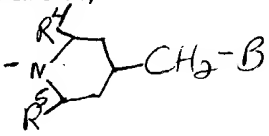
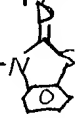
In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 1-18, drawn to the compound of formula I where R1 and R2 are H, Alkyl, alkenyl group, hydroxyalkyl group, cycloalkyl group, Z is  where R4 and R5 are H, or alkyl group, B represents  where D is S or O and R6 and R7 are all groups claimed, Q is –C(O), -C(=NOH)-, X is a monocyclic, or polycyclic cycloalkyl, or carbocyclic aryl group which may be substituted with an alkyl group, an aryl group, medicaments, classified in class 546, subclass 198.

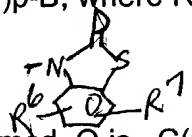
II. Claims 1-18, drawn to the compound of formula I where R1 and R2 are H, Alkyl, alkenyl group, hydroxyalkyl group, cycloalkyl group, Z is  where R4 and R5 are H, or alkyl group, B represents  where D is S or O and R6 and R7 are all groups claimed, Q is –C(O), -C(=NOH)-, X is 1, 2, 3, 4-tetrahydroisoqinoline, medicaments, classified in class 546, subclass 198.

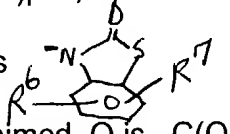
III. Claims 1-18, drawn to compound of formula I where R1 and R2 are H, Alkyl, alkenyl group, hydroxyalkyl group, cycloalkyl group, Z is  where R4 and R5 are H, or alkyl group, B represents  where D is S or O and R6 and R7 are all groups claimed, Q is –C(O), -C(=NOH)-, X is benzoisothiazole or benzoisooxazole, medicaments, classified in class 546, subclass 198.

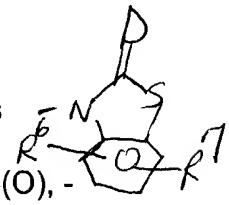
IV. Claims 1-18, drawn to compound of formula I where R1 and R2 are H, Alkyl, alkenyl group, hydroxyalkyl group, cycloalkyl group, Z is  where R4 and R5 are H, or alkyl group, B represents  where D is S or O and R6 and R7 are all groups claimed, Q is –C(O), -C(=NOH)-, X is cycloalkylsubstituted alkyl group, medicaments, classified in class 546, subclass 198.

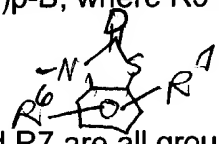
V. Claims 1-18, drawn to compound of formula I where R1 and R2 are H, Alkyl, alkenyl group, hydroxyalkyl group, cycloalkyl group, Z is  where R4 and R5 are H, or alkyl group, B represents  where D is NR8 wherein R8 is as claimed and R6 and R7 are all groups

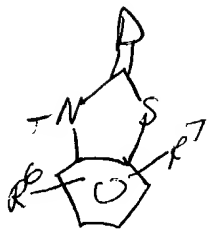
claimed, Q is –C(O), -C(=NOH)-, X is benzoisothiazole or benzoisooxazole, medicaments, classified in class 546, subclass 198.

VI. Claims 1-18, drawn to the compound of formula I where R1 and R2 are H, Alkyl, alkenyl group, hydroxyalkyl group, cycloalkyl group, Z is -N(R3)(CH2)p-B, where R3 Is as claimed, p is an integer of from 3 to 8, B represents  where D is S or O and R6 and R7 are all groups claimed, Q is –C(O), -C(=NOH)-, X is a monocyclic, polycyclic cycloalkyl group which may be substituted with an alkyl groups, medicaments, classified in class 548, subclass 181.

VII. Claims 1-18, drawn to the compound of formula I where R1 and R2 are H, Alkyl, alkenyl group, hydroxyalkyl group, cycloalkyl group, Z is -N(R3)(CH2)p-B, where R3 is as claimed, p is an integer of from 3 to 8, B represents  where D is S or O and R6 and R7 are all groups claimed, Q is –C(O), -C(=NOH)-, X is 1, 2, 3, 4-tetrahydroisoqinoline, medicaments, classified in class 548, subclass 181.

VIII. Claims 1-18, drawn to compound of formula I where R1 and R2 are H, Alkyl, alkenyl group, hydroxyalkyl group, cycloalkyl group, Z is -N(R3)(CH2)p-B, where R3 is as claimed, p is 3 to 8, B represents  where D is S or O and R6 and R7 are all groups claimed, Q is –C(O), -C(=NOH)-, X is benzoisothiazole or benzoisooxazole, medicaments, classified in class 548, subclass 181.

IX. Claims 1-18, drawn to compound of formula I where R1 and R2 are H, Alkyl, alkenyl group, hydroxyalkyl group, cycloalkyl group, Z is -N(R3)(CH2)p-B, where R3 is as claimed, p is 3 to 8, or alkyl group, B represents  where D is NR8 wherein R8 is as claimed and R6 and R7 are all groups claimed, Q is –C(O), -C(=NOH)-, X is benzoisothiazole or benzoisooxazole, medicaments, classified in class 548, subclass 181.

X. Claims 1-18, drawn to compound of formula I where R1 and R2 are H, Alkyl, alkenyl group, hydroxyalkyl group, cycloalkyl group, Z is -N(R3)(CH2)p-B, where R3 is as claimed, or alkyl group, B represents  where D is S or O and R6 and R7 are all groups claimed, Q is –C(O), -C(=NOH)-, X is cycloalkylsubstituted alkyl group, medicaments, classified in class 548, subclass 181.

XI. Claim 19 drawn to a sigma ligand comprising a substance selected from the group consisting of a compound and a salt thereof, and a hydrate thereof and a solvate thereof according to claim 1 where the compound is to one of groups I-X, class 546, 198.

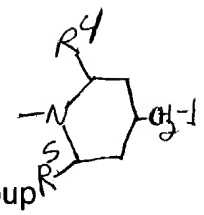
The Applicant traverses the election/restriction requirement made at paper no. 1203 asserting that the elected group I invention does not included the elected species. The revision to group I made in this action now includes the species. The applicant also asserts that groups were not formed in the restriction including Z groups that had the R3 moiety. The restriction requirement has been clarified in this action to also include

restricted groups where Z contains a R3 moiety. The applicant also traverses the restriction requirement alleging that the compounds contain the same or corresponding technical features.

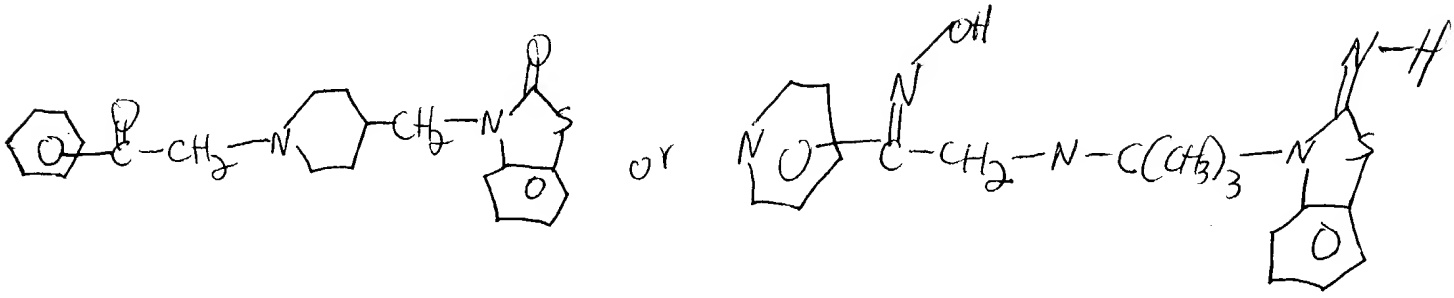
However, under PCT Rule 13.1: The international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention").

Applicant's instant claims do not relate to a single invention, specifically the application is drawn to multiple product inventions, and multiple methods of use inventions. Furthermore, the multiple inventions are not so linked as to form a single general inventive concept because according to PCT Rule 13.2:

> Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Applicant's instant claims do not contain a special technical feature. The compounds encompassed by the formula I: XQC(R1)(R2)Z do not contain a significant structural feature since, since the substituents on the technical feature vary extensively (for example, Q can be carbocyclic aryl or heterocyclic ring, Z can be -N(R3)(CH2)p-B or  , and R4 and R5 can come together to represent a 5- to 7-membered heterocyclic group

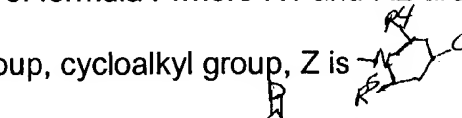
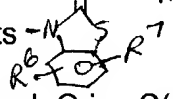
with other undefined intervening atoms) and when taken as a whole result in vastly different compounds (for example:



unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper and according to PCT Rule 13.3:

> The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

Therefore, since the claims do not contain a special technical feature, which defines a contribution over the prior art, i. e. WO2001025200, the examiner may determine within a single claim that the inventions are not so linked as to form a single general inventive concept. WO 2001025200 demonstrates that the X-QCR1R2 tail determines the utility of the molecule because when it is changed, then the compound's utility changes.

Claims 1-19, drawn to the compound of formula I where R1 and R2 are H, Alkyl, alkenyl group, hydroxyalkyl group, cycloalkyl group, Z is  where R4 and R5 are H, or alkyl group, B represents  where D is S or O and R6 and R7 are all groups claimed, Q is –C(O), -C(=NOH)-, X is a monocyclic, or polycyclic cycloalkyl group which may be substituted

with an alkyl group, an aryl group and medicaments have been examined below. The non-elected subject matter has been withdrawn from examination.

***Claim Objections***

Claim(s) 18 is/are objected to for being substantial duplicate of claim 17. When two claims in an application are duplicates, or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to reject the other as being a substantial duplicate of the allowed claim. M.P.E.P. 706.03(k). The intended use of the compounds and compositions of claim 18 carries no patentable weight and the claims are therefore duplicates of claim 17. This objection can be overcome by deleting claim 18.

**Rejections**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. A salt, hydrate thereof and a solvate are not

the same chemical species as the compound depicted in claim 1. In the absence of how to make hydrates and solvates of compounds of formula I and in the absence of a delineation of what salts, hydrates and solvates of the compounds depicted in claim 1 are being claimed, there is no umbrella coverage springing forth from the claimed compound of formula and the few examples of salts, hydrates and solvates depicted at page 22 and 23 of the specification.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for X equal to benzisoxazol-3-yl in the compound depicted in claim1, does not reasonably provide enablement for X equal to all heteroaryl groups, Y equal to any heteroaryl groups, or heteroaryl substituted alkyl groups, or R4 and R5 coming together to form any 5 to 7 membered heterocyclic group together with intervening atoms, and does not provide enablement for the use of the compound to prevent or treat any disease caused or promoted by the nerve controlling function of a sigma ligand. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It is also not established in the art to utilize pharmaceutical compositions to prevent disease.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,

3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

**The Nature of the Invention**

The nature of the invention in claims 1- 18 is novel compounds that act as a ligand for the sigma receptor/binding site and as medicaments comprising said compounds as an active ingredient.

**The State of the Prior Art**

The sigma receptor/binding site of the brain has been identified as an important target for the development of the antipsychotic drugs that are free from the side affects of currently available antipsychotic drugs having antagonistic activity on the dopamine D2 receptor (J. M. Walker and W. D. Bowen, F. O. Walker and R. R. Matsumoto, B. de Costa and K. C. Rice, Pharmacological Reviews, 42, pp. 355-402, 1990, See Reference U). The pharmacological significance, distribution, and functions of the sigma 2 binding site is relatively uncertain in the art, since a selective agent has not been available for this site, although recent studies have revealed that the sigma 2 site plays a role in controlling functions for the ileum (G. G. Kinney, E. W. Haris, R. Ray and T. J. Hudzik, Europ. J. Pharmacol., 294, pp. 547-554, 1995, See Reference V). Benzimdazolemethyl piperidine derivatives have been disclosed in WO 87/02359 (See Reference N), WO 8702035 (See Reference O), WO/8702666 (See Reference P) and US Patent No. 4215119 (See Reference A). But none of these publications have the benzothiazoline ring and have not been examined for their affinity for the sigma binding site. WO

96/05185 (See Reference Q) which notes Rocher, Jean-Philippe as the inventor, does disclose compounds that exhibit a high selectivity and a high affinity for the sigma –2-receptor but these compounds do not have the benzothiazoline ring.

**The predictability or lack thereof in the art**

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of Sigma receptor-mediated diseases, whether the Sigma-2 receptor was promoted or inhibited would affect the possible treatment of any disease.

Hence, in the absence of a showing of correlation between all the diseases disclosed as capable of treatment by the compound of claim 1 and the inhibition of Sigma-2 receptor, one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of Sigma-2 receptor, i.e. whether promotion or inhibition would be beneficial for the treatment of the diseases.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The

existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

**The amount of direction or guidance present**

The direction present in the instant specification is that the compounds of claim 1 can inhibit Sigma –2 receptors. However, the specification is silent and fails to provide guidance as to whether the diseases disclosed as Sigma-2-mediated diseases, require the inhibition of Sigma-2 receptor or the promotion of Sigma-2 receptor for treatment, i.e. the specification fails to provide a correlation between the diseases listed and the inhibition of Sigma-2 receptor. The applicant only provides binding assays for the instant compounds on Sigma-2-receptor; however, does not examine the pharmacological effects of these compounds on any of the diseases disclosed. Additionally no compounds where X is a heteroaromatic moiety other than benzisoxazol-3-yl in the compound depicted in claim1, Y is any heteroaryl group, or heteroaryl substituted alkyl groups, or R4 and R5 comes together to form any 5 to 7 membered heterocyclic group together with intervening atoms, have been tested in the Sigma –2 binding assay .

**The presence or absence of working examples**

There are no working examples for any diseases listed in the specification. Also, the compounds which are disclosed in the specification have no pharmacological data regarding the treatment of any disease. Also, the specification fails to provide working

examples as to how the disclosed diseases can be treated by the inhibition of Sigma-2, i.e. again, there is no correlation between the diseases listed and inhibition of Sigma-2.

Additionally no compounds where X is a heteroaromatic moiety other than benzisoxazol-3-yl in the compound depicted in claim1, Y is any heteroaryl group, or heteroaryl substituted alkyl groups, or R4 and R5 comes together to form any 5 to 7 membered heterocyclic group together with intervening atoms have been tested in the Sigma –2 binding assay .

**The breadth of the claims**

The breadth of the claims is that the compound of claim 1 can treat any disease, caused or promoted by the nerve controlling function of a sigma ligand.

**The quantity of experimentation needed**

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which disclosed diseases would be benefited by the inhibition of Sigma-2 receptor and would furthermore then have to determine whether the claimed compounds would provide treatment of the disease by the inhibition of Sigma-2.

**The level of the skill in the art**

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the claim 1 for the prevention or treatment of an any disease caused or promoted by the nerve controlling function of a sigma ligand. As a result necessitating one of skill to perform an exhaustive search for which Sigma-mediated diseases can be treated by the compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which Sigma-mediated diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, line 2, page 84 of the paper filed 2/2/04 and all other occurrences throughout the claims, the phrase "a salt thereof, and a hydrate thereof and a solvate thereof" is ambiguous. A compound can only contain one compound, not several compounds. Claims 1-18 are contradictory because they are simultaneously claiming a singular "compound" and yet "more than one compound" by claiming "a salt thereof, and a hydrate thereof and a solvate thereof". Is the applicant claiming a "compound" or a "mixture" which contains at least two or more compounds? Also, it is not clear as what hydrates or solvates of the compound the applicant is claiming.

B. In claims 17-18, page 87, lines 1 of the claims, the term "medicament" is indefinite because it is not a statutory class of invention. The phrase "pharmaceutical composition is suggested.

C. In claims 17-18, the phrase "substance" is indefinite and ambiguous. It is not clear what substance the applicant is claiming, since the substance is a mixture of the compound and an undefined salt, and an undefined hydrate thereof, and an undefined solvate thereof.

D. Claims 17-18 are indefinite because they are not written in the proper format for a pharmaceutical composition claim. By definition, a pharmaceutical composition claim must contain a reference to a pharmaceutically acceptable, inert carrier.

E. In claim 1, line 10, page 84 of the response filed 2/2/04, the phrase "with other intervening atoms" is ambiguous. What other intervening atoms are the applicants claiming?

The IDS filed 8/7/00 and 7/12/02 have been considered. The references in the IDS filed 8/7/00 that are in Japanese will not be considered until a translation is provided to the examiner.

The elected species is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

BMR
April 15, 2004

CEILA CHANG
PRIMARY EXAMINER
GROUP ~~1200~~ 1625